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## The influence of the lung and the liver on the pharmacokinetics and time course of action of neuromuscular blocking agents

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The use of curare in 25 patients by Harold Griffith and Enid Johnson in 1942 changed anesthetic practice throughout the world and heralded the start of the modern era of anesthesiology. The introduction of curare allowed adequate muscle relaxation at a lighter, and therefore better-tolerated, degree of general anesthesia. It would be hard to imagine if and how, without the introduction of neuromuscular blocking agents (NMBA's), open heart-, transplant-, or intracranial surgery could have developed.

Whereas the perioperative surgical and anesthetic conditions are greatly improved by the use of modern non-depolarizing NMBA's, anesthesiologists are still faced with two problems: how to secure the airway of a non-fasted patient rapidly using a non-depolarizing NMBA and how to prevent residual curarisation at the end of the surgical procedure. Both problems relate to aspects of the time course of action, i.e. the onset and the offset, respectively. Time course of action on its turn is mainly determined by the pharmacokinetics of the NMBA's since the interaction between NMBA's and the acetylcholine receptor is extremely fast and binding to the receptors almost immediately results in paralysis of the particular muscle fiber(s). Consequently, in order to understand the factors determining the onset and offset of block we have to know the factors that determine the pharmacokinetics of NMBA's. Therefore, our central question was: what happens following intravenous administration of a NMBA? The aim of the research described in this thesis was to investigate the influence of the lung and the liver on the pharmacokinetics and time course of action of NMBA's.

For several reasons, the lung is capable of influencing the early pharmacokinetics of NMBA's. Not only is the lung interposed between the site of drug administration and the site of effect, the lungs also receive the entire cardiac output and are equipped with the largest capillary surface area in the body. Because the lungs receive the entire cardiac output, even a small pulmonary extraction ratio could account for the transient storage of a significant part of the injected dose. Moreover, the lungs have shown to be able to (temporarily) store a variety of basic drugs, among which are opioids and propofol. Since NMBA's are basic amines it is possible that also NMBA's undergo pulmonary uptake and storage. Until now, the role of the lung in the pharmacokinetics of NMBA's has been neglected.

Therefore, we developed an isolated in situ heart-lung preparation in the cat to study this aspect of the disposition of NMBA's (Chapter 3). Validation of the model showed complete isolation of the organs without major biochemical changes or edema and a stable muscle response. Pilot experiments performed in this model showed a slow decay in the plasma concentration of rocuronium and Org 7617, making a prominent role for the lung in the pharmacokinetics of NMBA's unlikely.

To study the role of the lung in the onset of the neuromuscular blocking effect, we determined the pulmonary first-pass uptake of NMBA's. If substantial pulmonary first-pass uptake occurs, the question arises whether differences in potency and/or onset time between agents could at least to some extent be related to differences in pulmonary first-pass uptake. Therefore, the pulmonary first-pass uptake of five NMBA's, that have diverse potencies and/or onset times, were studied in the pig (chapter 4). Substantial first-pass uptake of rocuronium,

vecuronium, Org 9487, Org 7617 or *d*-tubocurarine by the lung did not occur. Since we selected NMBA's which differ in potency up to a factor of 30 and differ in onset time up to a factor of 2, this uptake study shows that differences in potency and onset time between NMBA's in vivo cannot, not even in part, be explained by differences in pulmonary first-pass uptake.

Since we chose to study the factors that determine the onset of action, the *early* pharmacokinetics of NMBA's should be unravelled in more detail. However, in pharmacokinetic and pharmacokinetic/pharmacodynamic (PK/PD) modelling studies the first blood sample (arterial or venous) is usually taken one or more minute(s) after drug administration. Since actual data on the *early* time course of the plasma concentration are lacking, investigators have to extrapolate the plasma concentration to time zero assuming instantaneous and complete mixing, and use this extrapolated plasma concentration profile for pharmacokinetic analysis and PK/PD modelling. For several reasons this extrapolation is incorrect. Therefore, we raised the following question: do plasma concentrations obtained from *early* arterial blood sampling improve PK/PD modelling? To answer this question we determined the influence of inclusion of experimental data obtained from *early* arterial sampling on PK/PD modelling. The concentration in the effect compartment at 50% block ( $EC_{50}$ ) based on extensive modelling of data obtained from *early* arterial sampling was calculated for a series of NMBA's. In addition, the  $EC_{50}$  derived from modelling was compared to the measured concentration in plasma during a steady state 50% block ( $Cp_{50SS}$ ) (Chapter 5). As expected, a high peak concentration in the arterial blood was seen within 20 s after administration of the NMBA. This confirmed that the mixing of the NMBA in the central volume of distribution is indeed far from complete. Extensive PK/PD modelling revealed that plasma concentrations obtained from *early* arterial blood sampling can improve PK/PD modelling. Independent of the type of modelling, the  $EC_{50}$  and  $k_{e0}$  (rate constant for equilibration with the effect compartment) based on data sets including *early* arterial blood sampling were, for all five NMBA's, significantly higher and lower, respectively, than those based on data sets obtained from usual sampling, i.e. from 1 or 2 min after administration of the NMBA. However, the goodness of fit was not entirely satisfactory, suggesting that the PK/PD model could not adequately describe the relationship between the rapidly changing plasma concentration during the first minute after administration and the effect. Usually, the Sheiner link model is used to correlate the concentration profile in the effect compartment to the modelled plasma concentration profile which is smoothened due to extrapolation of the plasma concentration to time zero. The true plasma concentration profile, however, is not smooth at all. Therefore, we developed an interstitial link model consisting of an effect compartment that is linked to an interstitial compartment interposed between the plasma compartment and the effect compartment. Although the interstitial link model improved the goodness of fit, there is an identifiability problem hampering the interpretation of the results. PK/PD analysis revealed that a parametric pharmacodynamic (sigmoid  $E_{max}$ ) model could not describe the time course of effect of the NMBA's adequately. Our results

may implicate that for PK/PD modelling, depending on the question to be answered, *early* arterial sampling should be considered.

With regard to the onset of neuromuscular block the liver plays an important role in the pharmacokinetics of NMBA's. The liver synthesizes plasma cholinesterase and other plasma esterases that play a crucial role in the enzymic degradation of some NMBA's. Thus far, the factors that determine the onset time are not fully known. On the basis of *in vitro* studies, differences in receptor affinity were suggested to account for the differences in onset time between NMBA's. Since a rapid decrease in the concentration of a NMBA in plasma, due to a high rate in early distribution or elimination of NMBA from plasma, results in a rapid equilibration of the NMBA between plasma and biophase, we hypothesized that the rate of decrease in the plasma concentration of a NMBA influences the onset time of neuromuscular block. To test the hypothesis, we inhibited the enzymic degradation of suxamethonium and of mivacurium by means of a selective plasma cholinesterase-inhibitor, thus decreasing the rate of disappearance of the NMBA from plasma (Chapter 6). The hypothesis was found to be valid: inhibition of the enzymic degradation of suxamethonium and mivacurium increased the onset time of block and decreased the  $ED_{70}$  of both agents. Therefore, pharmacokinetics influences the onset time of neuromuscular block. Our results imply that in order to obtain an ultrashort onset time, i.e. one minute or less, NMBA's should be developed which not only have a low affinity for the receptor, but also should disappear from plasma rapidly.

Also with regard to the offset of neuromuscular block, the liver is an important organ for the pharmacokinetics of NMBA's. Substantial amounts of many steroidal NMBA's are taken up into the liver and are excreted, either as unchanged compound or in the form of metabolites, into the bile. The role of the liver in the distribution, elimination and time course of action of NMBA's can be elucidated by temporarily excluding the liver from the systemic circulation by means of a portocaval shunt and clamping of the hepatic portal vein and common hepatic artery. We investigated 24 NMBA's in this liver shunt model in the cat (Chapter 2). Temporary exclusion of the liver from the systemic circulation demonstrated that the liver plays an important role in the distribution and/or elimination of NMBA's. Exclusion of the liver prolonged the duration to 90% recovery of all of the investigated NMBA's. Similar experiments in the pig with additional sampling of blood showed that exclusion of the liver prolonged the duration of action to 90% recovery and at the same time decreased the rate of plasma concentration decay of rocuronium. When the normal circulation was restored, i.e., the liver included in the systemic circulation, the plasma concentration decreased rapidly. In the search for physico-chemical properties promoting hepatic uptake, a trend was found for the more lipophilic agents to be taken up by the liver more extensively than the less lipophilic agents. No trend was found between the degree of protein binding of the NMBA's tested and their hepatic uptake.

In humans, however, such a study cannot be performed: alternatively, controlled hypothermia, a condition frequently applied in human patients, could be used to investigate the role of the liver in the offset of neuromuscular block. It has

long been recognized that hypothermia prolongs the time course of action of non-depolarizing NMBA's. The various mechanisms that may underly this prolongation, however, are not known. Since the time course of action of NMBA's, i.e. pharmacokinetics and/or pharmacodynamics, is mainly determined by a redistribution process, a major contribution of a pharmacokinetic mechanism to this phenomenon should be considered. We therefore hypothesized that the hypothermia-induced prolongation of the time course of these NMBA's results from a change in their pharmacokinetics, i.e. a reduced plasma clearance. To test our hypothesis, we determined the influence of hypothermia (surface cooling) on the time-course of action and on the pharmacokinetics of rocuronium in humans (Chapter 7). Hypothermia prolonged the duration of action of rocuronium and delayed its spontaneous recovery of block. Altered pharmacokinetics, i.e., a decreased plasma clearance in the hypothermic patients in combination with an unchanged volume of distribution, can explain the prolongation of the duration of action. Consequently, the dose requirement of rocuronium under hypothermia is largely decreased, which makes dosing based on the results obtained from monitoring of the muscle response obligatory.

If hypothermia prolongs the time course of action of NMBA's via an effect on the pharmacokinetics, does perturbation of the liver uptake then play a role in this change in pharmacokinetics? or, Is the pharmacokinetic change based on a reduced rate of extrahepatic distribution, for instance due to a reduced cardiac output and muscle blood flow and/or on a reduced rate of metabolism? To elucidate the mechanism of the hypothermia-induced prolongation of NMBA's, we used an isolated perfused rat liver model in which the liver perfusion rate can be maintained fairly constant and other organs that are important for distribution or elimination are absent. Since in clinical practice, hypothermia may occur either alone or in combination with acidosis or hypoxia we also investigated the influence of these conditions on the net hepatic uptake, i.e. the difference between uptake and release, and on the biliary excretion of vecuronium. In addition, we determined the influence of temperature on the metabolic conversion of vecuronium in bile and liver homogenate. Since uptake in mitochondria is an important aspect of hepatic storage, we also studied the influence of hypothermia on the uptake of vecuronium in isolated rat liver mitochondria. Finally, computer-aided simulations were performed in order to analyze the observed changes and to study the relative influence of these conditions on the hepatic net uptake, metabolism and biliary excretion (Chapter 8). Hypothermia and acidosis both reversibly reduced the net uptake of vecuronium by the liver. Hypothermia also reduced the rate of vecuronium metabolism. Hypoxia only slightly, but irreversibly, reduced the net uptake but largely affected biliary excretion. Interestingly, whereas hypothermia reduced the net uptake of vecuronium in the liver extensively, its biliary excretion virtually remained intact. Apparently, the reduction in the rate of metabolism results in maintaining the concentration of the parent compound in the liver in spite of the decreased uptake rate, thus maintaining the concentration gradient between liver and bile. Due to the reduced conversion of vecuronium to its 3-desacetyl metabolite, hypothermia led to a drastic reduction in the biliary excretion rate of 3-

desacetyl vecuronium. Reasonable fits in the hypothermia experiments and to a lesser extent in the acidosis experiments, could only be obtained when the rate constants for hepatic uptake and metabolism of vecuronium were allowed to decrease during the period of hypothermia or acidosis. The effects of acidosis may have been due to a pH-induced increase in the degree of protonation of the tertiary amino group of vecuronium, which could have reduced the efficacy of carrier-mediated transport. In the hypoxia experiments, reduction of the concentration of oxygen in the gassing mixture to only 70% did not lead to gross deterioration of liver function according to the usual viability criteria. However, biliary excretion of vecuronium was lowered abruptly and extensively while excretion was not resumed at returning to normal oxygenation. Most likely, irreversible liver damage had occurred specifically reflected in perturbation of the biliary excretion step.

The total recovery of vecuronium from perfusion medium, bile and liver at the end of the experiment was 72% (61 – 86) for all liver perfusions, and did not differ in the control, hypothermia, acidosis or hypoxia experiments. This recovery value is significantly lower than reported in other studies. Our steady state/continuous infusion study design, however, differed from the single bolus studies that are commonly employed. We speculated that the persistent presence of the NMBA in the liver could lead to storage in a deep (non-extractable) compartment. By means of bolus administration of vecuronium in additional liver perfusion experiments, we obtained the same high total recovery as other investigators and we showed that the storage process only temporarily prevents the drug from being extracted. This isolated perfused rat liver study shows that hypothermia extensively, and acidosis to a lesser extent, influences the pharmacokinetics of vecuronium and emphasizes the need for effect measurement of NMBA's in patients during hypothermia to prevent overdosing.

Collectively, the data presented in this thesis indicate that the lung does not have a prominent role in the pharmacokinetics and time course of action of NMBA's. In contrast, the liver plays a prominent role in the pharmacokinetics of many NMBA's and is an important factor in both the onset and offset of block, either by synthesizing plasma cholinesterase that catalyzes the degradation of some NMBA's or by rapid hepatic uptake, metabolism or biliary excretion of other NMBA's.